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(54) Title: COMBINATION OF P53 GENE AND E1B-DELETED P53 GENE

(57) Abstract: The present invention uses the combination of the wild-type p53 gene and the E1B-deleted p53 gene which, hitherto, had not been considered scientifically justified because the over-expression of p53 would inhibit the AdE1B-deleted virus replication and, therefore, the killing of the cells. The combination has been shown to be more effective in killing cancer cells than the individual components used separately. It has been claimed in the medical literature that the Adenovirus vector, ONYX-015, which has a deletion in the E1B region, can selectively replicate in, and kill, human cancer cells that lack functional p53, but is non-cytotoxic to cells that have an intact (wild-type) p53. Recent evidence has contradicted this claim and suggested that ONYX-015 can replicate in cancer cells with wild-type p53 and that cells lacking p53 function are resistant to adenovirus-induced cell death. Functional p53 is deficient in over half of human cancers and its absence is thought to be a major factor in the pathogenesis of many malignant conditions. Many of the current cancer gene therapy protocols are using either wild-type p53 (Adwtp53) or the E1B-deleted variant (AdE1B), and usually only include patients with p53 mutations. However, these studies have only shown limited benefit, with many patients having stable disease, but few showing tumour regression. To improve the efficacy of gene therapy for cancer it is important to determine the true significance of the p53 status in cancer cells.

COMBINATION OF P53 GENE AND E1B-DELETED P53 GENE

The p53 gene is a very popular molecule in modern medicine, with extensive research being done to characterise the gene and numerous scientific articles written on the subject.

P53 is a 53 kilodalton phosphoprotein involved in several important mechanisms, such ascell cycle regulation, cell differentiation, DNA synthesis and repair, and apoptosis. It is a transcription factor that binds as a tetramer to a DNA sequence composed of two head-to-head repeats. The p53 gene is the most common target for genetic alteration across all types of human cancers; it is a tumour suppressor gene, but in its mutated form it seems to act also as an oncogene.

The p53 gene is located on the short arm of chromosome 17 and contains 11 exons interrupted by 10 introns. In mammals its organization is similar, with the exception of the rat in which intron 6 is missing. In human, the messenger RNA codes for a 394 amino acid protein, which is expressed in all tissues in a relatively low level.

The gene is very rich in G/C (guanine:cytosine), which implies that the gene evolves under the base compositional restraints. In about one quarter of all p53 mutations in human cancers are transitions at the CpG nucleotides.

Onyx-015 is an attenuated E1B-deleted adenovirus which does not produce a

55kD protein normally formed by the wild-type adenovirus. The protein inactivates wild-type p53 inside a host cell during infection. In this way the virus replicates and causes cytolysis of the infected cells. The E1B-deleted variant fails to inactivate the p53, no viral replication can take place inside the cell, and an abortive infection results. If a cell lacks p53, or has a mutant, non-functioning p53, the 55kD protein is not required to inactivate p53 and the virus will replicate and produce cytolysis. This is the rationale for using Onyx-015 in gene therapy protocols. However, it is of no use in cancer cells that are expressing wild-type p53.

Alternative gene therapy strategies have used adenoviral vectors expressing wild-type p53. This is based on studies that showed that transfection of tumour cells with plasmid DNA expressing wild-type p53 or infection with retrovirus expressing wild-type p53 was cytotoxic to cells expressing mutant p53.

Thus, the existing scientific evidence shows that gene therapy with either wild-type p53 or with the E1B-deleted p53 is active only against tumors that express the mutant or depleted p53 gene.

This present invention is unique in that it combines the wild-type p53 adenovirus and the E1B deleted adenovirus and that this combination is cytotoxic to tumour cells that express wild-type p53 and to those with mutant p53. Thus, this present invention provides a method of enhancing and increasing the cytotoxic effects of gene therapy with adenoviral vectors.

The status of p53 expression within cancer cells is of considerable clinical significance because a large number of cancers do not express mutant p53 or are

p53 deleted. Such cancers do not respond well to current gene therapy regimens. Furthermore, most cancers have a mixture of cells, some expressing mutant or deleted p53, and others expressing wild-type p53. Thus, gene therapy protocols which are aimed at mutant p53 will be only partially successful.

In most wild type adenoviruses the EIB-55kD protein inactivates wild-type p53 inside a host cell during infection. In this way the virus replicates and causes cytolysis of the infected cells. The EIB-deleted adenovirus variant fails to inactivate the p53 in cells expressing wild type p53. In cancer cells with a mutant or a nonfunctioning p53, the 55kD protein is not required to inactivate p53 and therefore Ad EIB deleted virus will replicate and produce cytolysis. This is the rationale for using Ad BIB deleted (Onyx-015) in gene therapy protocols. However, it is of no use in cancer cells that are expressing wild-type p53.

Alternative gene therapy strategies have used adenoviral vectors expressing wild type p53. This is based on studies that showed that transfection of tumour cells with plasmid DNA expressing wild-type p53 or infection with retrovirus expressing wild-type p53 was cytotoxic to cells expressing mutant p53.

Thus, the existing scientific evidence shows that both gene therapy approaches, with either wild-type p53 or with the E1B deleted p53, are active only against tumours that express the mutant or depleted p53 gene.

The status of p53 expression within cancer cells is of considerable clinical significance because a large number of cancers do not express mutant p53 and have no p53 deletion. Such cancers do not respond well to current gene therapy regimens. Furthermore, most cancers have a mixture of cells, some expressing

mutant or deleted p53, and others expressing wild-type p53. Tumours are heterogeneous in nature. Thus, gene therapy protocols which are aimed at mutant p53 will be only partially successful.

In this study a series of hepatocellular cancer cell lines were transfected with Adwtp53 and it produced a cytotoxic effect in the Hep3B cells (deleted p53), partially cytotoxic in the PLC/PRF/5 cells (mutated p53), but there was no inhibition of HepG2 cells (wild-type p53). The doses of Adenovirus used were large. In these tumour cell lines the use of Adwtp53 was only effective in those cells expressing mutant or deleted p53.

The same cell line types, as above, were transfected, in separate experiments, with AdEIB. The E1B-deleted adenovirus selectively inhibited Hep3B (deleted p53) and PLC (mutated p53), but again failed to inhibit HepG2 (wild-type p53). The doses of Adenovirus used were also large.

In a third series of experiments, a combination of Adwtp53 and AdE1B-deleted virus was used to transfect the hepatocellular cancer cell lines. The combination lead to major cytotoxicity to all cancer cell lines, irrespective of the p53 status. In addition, when all three cell lines were grown together, mimicking the cell mixture typically expected in human cancers, there was a complete cytotoxic effect, with total cell death. Furthemore, the cytotoxic effect was seen with a viral concentration less than that required for each virus individually even at 1 pfu/cell concentration.

This invention shows the combination of an adenovirus vector expressing wild-type p53 and an adenovirus expressing E1B-deleted p53 is effective in killing

cancer cells that express mutant or deleted p53 and also cells expressing wild-type p53 and at very low concentration. The invention describes a new therapeutic approach, based on the simultaneous use of an adeno-associated virus competent in replication with an adeno-associated virus encoding p53.

A series of hepatocellular cancer cell lines were transfected with Adwtp53 and it produced a cytotoxic effect in the Hep3B cells (deleted p53), partially cytotoxic in the PLVC cells (mutated p53), but there was no inhibition of HepG2 cells (wild type p53). The doses used were not excessive. In these tumour cell lines the use of wtp53 was only effective in those cells expressing mutant or deleted p53.

The same cell line types, as above, were transfected, in separate experiments, with AdE1B. The E1B-deleted adenovirus selectively inhibited Hep3B (deleted p53) and PLC (mutated p53), but failed to inhibit HepG2 (wild-type p53).

In a third series of experiments, a combination of Adwtp53 and AdE1B-deleted virus was used to transfect the hepatocellular cancer cell lines. The combination led to complete cell death in all cell lines, irrespective of the p53 status. In addition, when all three cell lines were grown together, mimicking the cell mixture typically expected in human cancers, there was a complete cytotoxic effect, with total cell death. Furthermore, the cytotoxic effect was seen with a viral concentration 2 log less than that required for each virus individually.

This invention allows for the combination of a combination of an adenovirus vector expressing wild-type p53 and an adenovirus expressing E1B-deleted p53. This combination is effective in killing cancer cells that express mutant or deleted p53 and also cells expressing wild-type p53. Therefore, the invention allows a

new therapeutic approach to cancer treatment, based on the simultaneous use of both viruses for the treatment of cancer in humans and animals.

METHODS

HepG2 hepatoma cells, which express wild type p53, PLC/PRF/5 hepatoma cells, which express mutant p53 (codon 249), Hep3B hepatoma cells, which are p53-null, Nasal septum fibroblast cells, Chang liver and human hepatocytes, which all express wild-type p53, were grown in Dulbecco's modified Eagle medium (DMEM, GIBCO/BRL) supplemented with 10% foetal bovine serum at 37°C an 10% CO_2.

AD E1B deleted contains an 827-bp deletion in the region encoding the 55-kDA protein in combination with a stop codon to ensure that a truncated 55-kDA product cannot be expressed.

In cytotoxicity assays 10^3 cells were fed to each well of a 96-well plate 24 hours before infection. Cells were infected with AD E1B deleted or Ap53 at MOI 1, 10, 100 in a total volume of 200µl DMEM + 2% FBS. After incubation at 37°C for two days, cells were washed with PBS and infected with different concentrations of Ad E1B deleted or Ad-p53 for another two days. At day 4, cytotoxicity effect was determined by colorimetric assay as described by Shekan et al., (1990). Briefly, cells were fixed in 10% trichloracetic acid for 60 mins. at 4°C. Fixed cells were stained with 100µl sulphorhodamine B or 10 mins., rinsed five times with 1% acetic acid and the dye solubilised for 1 hour with 200µl unbuffered Tris base. The relative survival of cells was calculated by comparing the OD 560nm

readings of the infected cells with the readings of the uninfected cells, using a plate reader.

RESULTS

In the experiments to study the cytotoxic effect induced by E1B deleted, at MOI 100 approximately 40% of Hep3B cells (p53-null) were killed by Ad E1B deleted, whereas less than 20% of HepG2 (wt-p53) or PLC/PRF/5 (mut-p53) cells were killed (Figure 1).

At MOI 1, a combination of Ad-p53 and Ad E1B deleted caused death of 73% of Hep3B cells, 60% of HepG2 and PLC/PRF/5 cells, but only 30% 0f fibroblasts (Figures 2 & 3). The cell death rate is significantly greater ($p<0.01$) for the combination of E1B deleted and Ad-p53 than for Ad-p53 alone.

Tables 1 & 2 show that Ad E1B deleted, Ad Null and Ad E1B are not toxic to HepG2 cell lines at 1 an 10 pfus/cell concentrations. However, when Ad E1B deleted and Ad p53 were mixed together the combination was highly cytotoxic, even at concentrations as low as 1 pfu/cell.

CLAIMS

1 A combination of wild-type p53 gene and the E1B-deleted p53 gene given simultaneously to produce a cytotoxic effect in human and animal cancer cells.

2 A combination of wild-type p53 gene and the E1B-deleted p53 gene given sequentially to produce a cytotoxic effect in human and animal cancer cells.

3 A combination of wild-type p53 gene and any adeno-associated virus competent in replication given either simultaneously or sequentially to produce a cytotoxic effect in human and animal cancer cells.

4 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using an adenovirus vector to transport the combination of genes.

5 A combination of wild-type p53 and an adeno-associated virus competent in replication given sequentially or simultaneously, as in 3 above, using an adenovirus vector to transport the combination of genes.

6 A combination of wild-type p53 and an adeno-associated virus competent in replication given sequentially or simultaneously, as in 3 above, using an liposomal vector to transport the combination of genes.

7 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2 above, using a liposomal vector to transport the combination of genes.

8 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using any vector carrying the E1A gene to transport the combination of genes.

9 A combination of wild-type p53 and an adeno-associated virus competent in replication given sequentially or simultaneously, as in 3,5 & 6 above in which the adeno-associated virus competent in replication has the E1A gene or encodes for the E1A depleted gene.

10 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by the intravenous route.

11 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by the oral (cochleate) route.

12 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by the intraperitoneal route.

13 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered directly into the tumour.

14 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by the intra-arterial route.

15 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by any of the routes described in 6,7,8,9,&10, and used to kill human and animal cancer cells expressing a mutant p53 gene.

16 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by any of the routes described in 6,7,8,9,&10, and used to kill human and animal cancer cells with a deleted p53 gene.

17 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by any of the routes described in 6,7,8,9,&10, and used to kill human and animal cancer cells expressing the wild-type p53 gene.

18 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1&2, using a vector, as in 3,4,&5, administered by any of the routes described in 6,7,8,9,&10, and used to kill human and animal cancer cells expressing a combination of forms and expressions of p53 gene, including, but not exclusively, a combination of the forms and expressions described in 11, 12, &13.

19 A method of using the invention whereby the adenovirus E1B-deleted form is used first and wild-type p53 is added to the vector

20 A method of using the invention, as in 1& 2, whereby plasmid p53 and the gene encoding R1A are used in combination or sequentially.

21 A method of using the invention, as in 1,2, 11,12,13, & 14, and administered in ways described in Claims 6-10, whereby plasmid wild-type p53 and the gene encoding E1A are used in combination or sequentially with the E1A gene either as a plasmid or in a vector.

22 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1,2, 11,12,13, & 14, and administered in ways described in Claims 6-10, using a retrovirus vector to transport the combination of genes or the genes sequentially.

23 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1,2, 11,12,13, & 14, and administered in ways described in Claims 6-10, using a Herpes virus vector to transport the combination of genes or the genes sequentially.

24 A combination of wild-type p53 and the E1B-deleted p53 given sequentially or simultaneously, as in 1,2, 11,12,13, & 14, and administered in ways described in Claims 6-10, using fusion proteins to transport the combination of genes or the genes sequentially.

TABLES & FIGURES

Table 1 Percentage survival of HepG2 cells with varying concentration of AdE1B deleted cells and constant concentration of 1 pfu/cell of Ad p53 or Ad Null.

PFU/cell	AdE1B deleted	Ad p53	Ad Null
0	100	138.988	89.846
1	91.379	14.866	45.774
5	75.109	14.317	23.454
24	36.253	13.851	16.353
120	9.178	9.133	7.174

Table 2 Percentage survival of HepG2 cells with varying concentration of AdE1B deleted cells and constant concentration of 10 pfu/cell of Ad p53 or Ad Null.

PFU/cell	AdE1B deleted	Ad p53	Ad Null
0	100	88.97	108.308
1	91.379	10.556	83.673
5	75.109	8.958	32.574
24	36.253	6.181	13.108
120	9.178	5.046	8.687

Figure 1. Ad E1Bdeleted induced cytotoxic effect.

Hep3B (p53-null), HepG2 (wt-p53), PLC/PRF/5 (mut-p53) and fibroblasts cells were infected with Ad E1B deleted at MOI 1,10, 100.

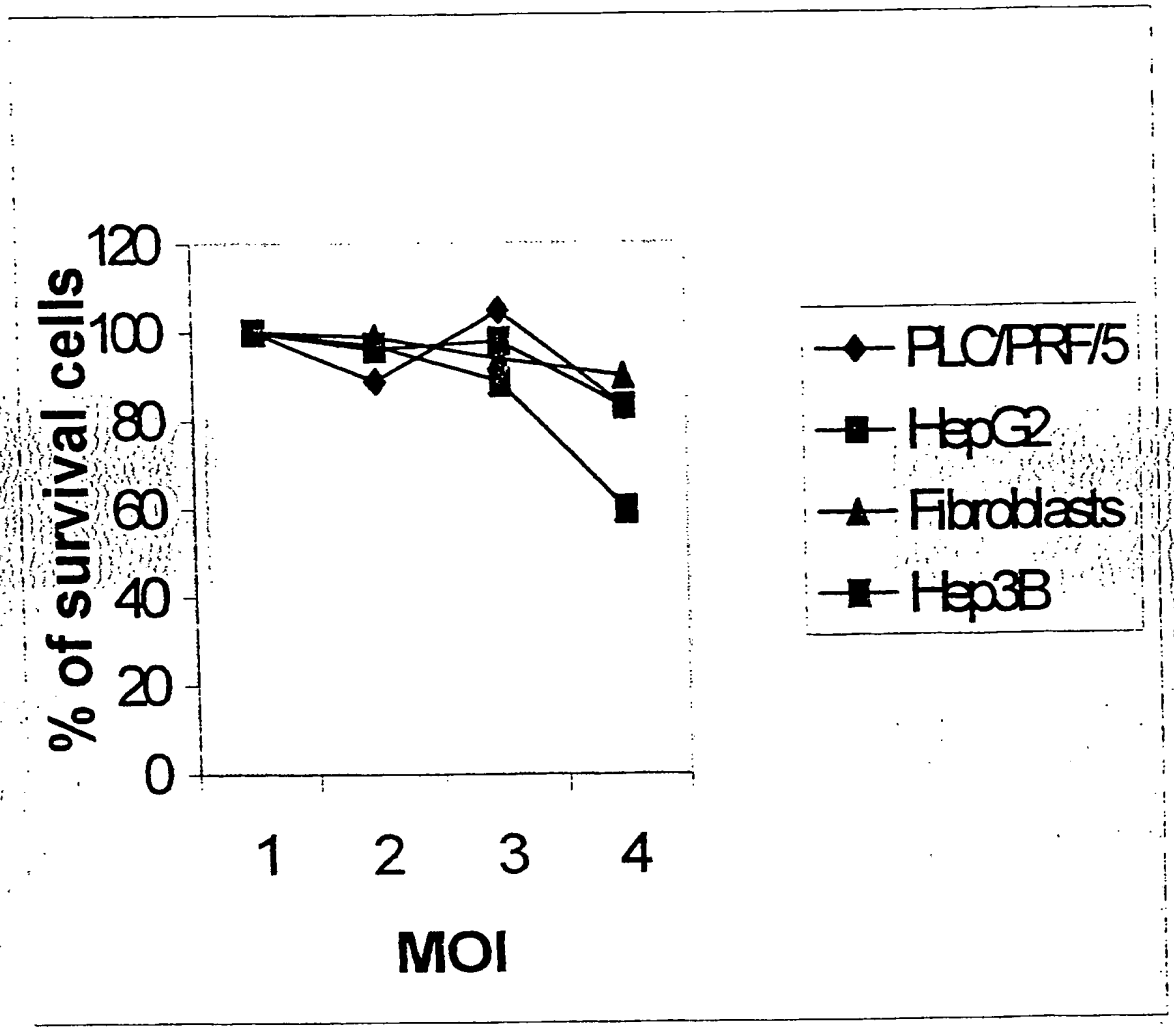
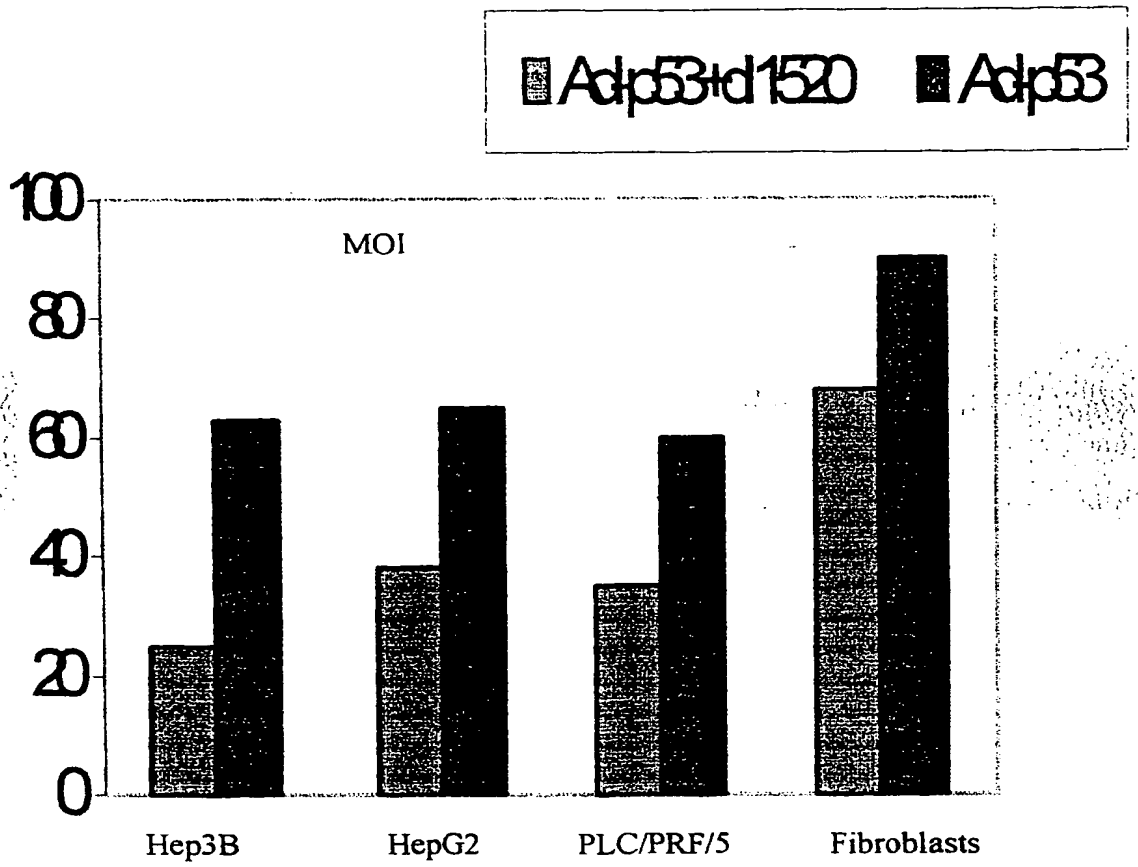


Figure 2. Ad-p53 enhanced cytotoxic effect of Ad E1B deleted on HCC cell lines. Cells were infected with Ad-p53 two days before Ad E1B deleted infection. Two days after Ad E1B deleted infection cytotoxic assay was performed using SRB staining



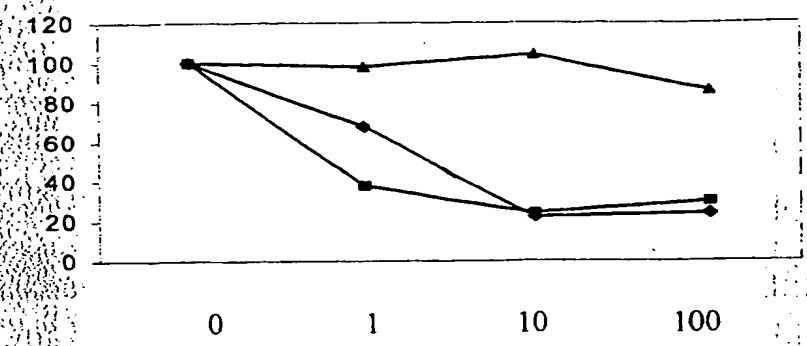


Figure 3a

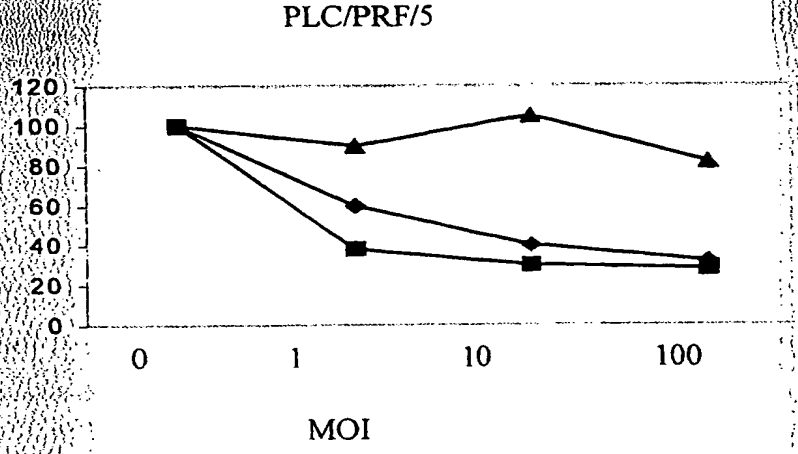


Figure 3b

Figure 3c

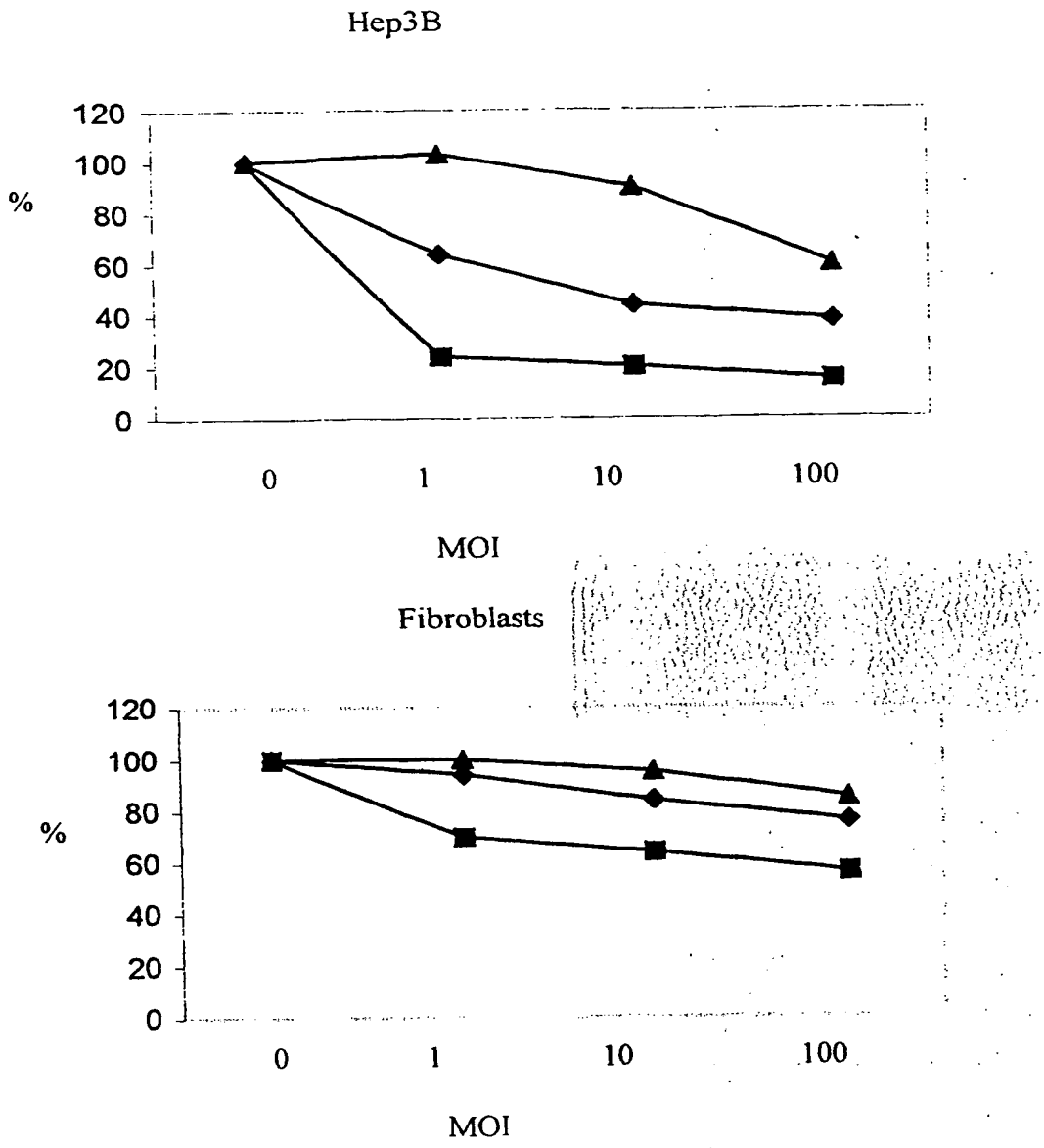


Figure 3d

Figures 3a - 3d Hep3B, HepG2, PLC/PRF/5 cells and fibroblasts were infected with different MOI adenovirus. Cytotoxic assay using SRB staining was performed and relative survival cells were calculated by comparing the OD 560nm readings of infected cells with the mock infected cells. ▲—▲ Ad E1B deleted four days, ♦—♦ Ad-p53 f our days, ■—■ Ad-p53 two days

INTERNATIONAL SEARCH REPORT

Intern[illegible]pplication No
PCT/GB 00/01266

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K48/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, MEDLINE, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHAO J ET AL: "p53 enhanced the antitumoral efficacy of E1B 55-Kilodalton mutant adenovirus on hepatocellular carcinoma cell line." GUT, vol. 44, no. SUPPL. 1, April 1999 (1999-04), page A87 XP000971890 British Society of Gastroenterology Annual Meeting;Glasgow, Scotland, UK; March 23-25, 1999 ISSN: 0017-5749 the whole document ---	1-24
E	GB 2 342 042 A (WOOD CHRISTOPHER BARRY) 5 April 2000 (2000-04-05) the whole document ---	1-24
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2001	24 01 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Niemann, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ROTHMANN T ET AL: "Replication of ONYX-015, a potential anticancer adenovirus, is independent of p53 status in tumor cells" JOURNAL OF VIROLOGY, December 1998 (1998-12), XP002139587 the whole document ---	
A	WO 97 30732 A (ONYX PHARMA INC) 28 August 1997 (1997-08-28) the whole document ---	
A	WO 99 59604 A (ONYX PHARMA INC) 25 November 1999 (1999-11-25) the whole document ---	
A	WILLS K N ET AL: "DEVELOPMENT AND CHARACTERIZATION OF RECOMBINANT ADENOVIRUSES ENCODING HUMAN P53 FOR GENE THERAPY OF CANCER" HUMAN GENE THERAPY,XX,XX, vol. 5, no. 9, 1 September 1994 (1994-09-01), pages 1079-1088, XP000579605 ISSN: 1043-0342 the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/01266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-24 partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-24 partially

The claims lack clarity (Article 6 PCT). This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, supported and disclosed, namely those parts relating to the combination of a vector encoding p53 and a E1B region deleted adenovirus.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. Application No
PCT/GB 00/01266

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2342042 A	05-04-2000	NONE	
WO 9730732 A	28-08-1997	US 6133243 A	17-10-2000
		AU 721970 B	20-07-2000
		AU 2276597 A	10-09-1997
		CA 2241142 A	28-08-1997
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